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Reaction mechanisms in peptide synthesis. Part 1. Semiquantitative characteristics of the reactivity of 2-methyl-5(4*H*)-oxazolone with water and ammonia in the gas phase and weakly polar media

Jerzy Ciarkowski*, Francis M.F. Chen and N. Leo Benoiton**

Department of Biochemistry, Faculty of Medicine, University of Ottawa, Ottawa, Ont., Canada K1H 8M5

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SUMMARY

2,4-Dialkyl-5(4*H*)-oxazolones are well-recognized intermediates in some aminolysis reactions in peptide synthesis. Using the MOPAC molecular orbital programs, detailed geometric and energetic characteristics of the elementary reaction pathways for the additions of water and ammonia to 2-methyl-5(4*H*)-oxazolone have been determined at the AM1 level. The results demonstrate that the additions must be parsed into a two-step mechanism involving formation of the α-hydroxyimine followed by tautomerization to the parent *N*-acetylamino acid or amide.

INTRODUCTION

Peptide-bond formation between two amino acid residues involves nucleophilic attack at the carbonyl of the carboxy-containing component by the amino group of the second component. Reaction is facilitated by 'activation', or enhancement of the electrophilicity of the target atom, which may be achieved by conversion of the carboxy-group to an *O*-acylisourea, ester, azide, anhydride, etc. [1]. Activation, however, engenders with it a proclivity to a competing intramolecular cyclization reaction involving attack by the oxygen atom of the acylamino group of the adjacent peptide bond or *N*-protecting group, generating an oxazolone (2,4-disubstituted-5(4*H*)-oxazolone or 5-oxo-4,5-dihydro-1,3-oxazolone) [2]. Oxazolones are a productive form of the activated

*On leave from the University of Gdansk, Poland.
**To whom correspondence should be addressed.

residue, but are also the source of the epimerization which sometimes occurs at the activated residue. Oxazolones [3] and anhydrides [4] are stable enough to be isolated and purified. Knowledge of their properties and mechanisms of reaction forms an integral part of the understanding of peptide-bond formation.

Our interest in the chemistry of peptide synthesis has prompted us to examine the recently developed molecular orbital methods as a source of information on the mechanisms of reactions implicated in peptide synthesis. The present work is the first of an intended series on the subject. Recognizing that the models to be addressed would be of considerable size, we chose to begin with the semiempirical molecular orbital method AM1 [5], that is believed to generate relatively reliable results at reasonable cost [6]. Indeed, there are several recent reports of success with the method [7], in particular for treating hydrogen bonding [8], which is critical to our undertaking. As a start, we chose the elemental reaction of 2-methyl-5(4*H*)-oxazolone (whose precursor is *N*-acetylglycine) with the simplest oxygen and nitrogen nucleophiles, water and ammonia. This choice seemed appropriate to test the selected software and to acquire experience and reference data at a reasonable expense of computer time as a preliminary to future dealings with more complicated chemical models.

MATERIALS AND METHODS

Computing was done on the University of Ottawa IBM-compatible Amdahl 5860 mainframe computer that is managed by the VM/CMS operating system, using the General Molecular Orbital Package MOPAC, version 4.01 [9]. The molecular images were prepared by use of either the PCMODEL or PCDISPLAY program, supplied by Serena Software (Bloomington, IN), on a PC AT-compatible desktop computer. Both programs can directly accommodate the data formats typical of MOPAC. The MOPAC results are assigned decisive quality in some cases. It should be remembered that the performance of MOPAC is sometimes questioned, e.g. [10].

RESULTS AND DISCUSSION

Gas-phase calculations

Since each of the semiempirical methods included in MOPAC has been parametrized against experimental values of heats of formation (HoF) at standard conditions (1 at 25°C), the results of the HoF calculations presented below refer to the gas phase.

The only analogous structure obtained by any of the diffraction methods that has been published is that of 2-phenyl-4-(*Z*-1′-ethoxyethylidene)-5-(4*H*)-oxazolone obtained by X-ray analysis [11]. This molecule, however, is of limited comparative value because it contains an extensive π-electron system comprising all of the ring except the oxygen atom, while the ring in our model contains two distinctly separated double bonds. Therefore, we assumed an initial geometry of 2-methyl-5(4*H*)-oxazolone using typical values for its initial bond lengths and angles, and assumed that MOPAC would correctly refine them. Refined geometries were obtained by means of all three MO methods i.e., MINDO/3, MNDO and AM1. The 2-methyl-5(4*H*)-oxazolone ring is practically planar, with the methyl group being free to rotate with a virtually negligible threefold energy barrier equal to ≈ 0.04 kcal/mol. For the reasons stated in the Introduction, subsequent discussion refers exclusively to use of the AM1-method. The AM1 geometry, charge distribution and

TABLE I
A CONCISE PROTOCOL FROM THE AM1 OPTIMIZATION OF THE REACTANTS[a]

Summary of AM1 calculation version 4.01	Heat of formation	=	−50.302234 kcal/mol
C4 H5 N O2	Dipole	=	2.27370 Debye
2-methyl-5(4*H*)-oxazolone (optimized)	No. of filled levels	=	19
	Ionization potential	=	10.912070 eV
	Molecular weight	=	99.089

	Final geometry obtained							Connectivities			
No	AM1 Symmetry precise							N1	N2	N3	Charge
1	C	0.000000	0	0.000000	0	0.000000	0	0	0	0	−0.1463
2	XX	1 000000	0	0 000000	0	0.000000	0	1	0	0	
3	C	1.527174	1	52.295164	1	0.000000	0	1	2	0	0.2663
4	N	1.460225	1	52 295164	0	180.000000	0	1	2	3	−0.1994
5	C	1.308537	1	108 037582	1	−0.020142	1	4	1	3	0.0862
6	O	1.423192	1	114.579605	1	0.036950	1	5	4	1	−0.2415
7	C	1.479318	1	131.418054	1	−179.660176	1	5	4	1	−0.1631
8	H	1.118577	1	109.322391	1	−132.388843	1	7	5	4	0.1158
9	H	1.119042	1	109 043220	1	108.860632	1	7	5	4	0 1149
10	H	1 117356	1	110.696880	1	−11.523269	1	7	5	4	0.1173
11	H	1.122101	1	110.517225	1	−119.460361	1	1	4	5	0.1514
12	H	1.122111	1	110 514587	1	119.395629	1	1	4	5	0 1513
13	O	1.217137	1	136.272223	1	179.997510	1	3	1	4	−0.2528

	AM1 symmetry, T = 280									
No.	Water optimized geometry							N1	N2	N3
1	O	0.000000	0	0.000000	0	0.000000	0	0	0	0
2	H	0 961267	1	0.000000	0	0 000000	0	1	0	0
3	H	0.961267	0	103.531656	1	0.000000	0	1	2	0
Exp.[b]	0.958–0.972		104.5–104.8							
Theor.[c]	0.941–0.968		104.1–106.0							

	AM1 symmetry, T = 280									
No	Ammonia optimized geometry							N1	N2	N3
1	N	0.000000	0	0.000000	0	0.000000	0	0	0	0
2	H	0.997214	1	0.000000	0	0.000000	0	1	0	0
3	H	0 997214	0	109.353116	1	0.000000	0	1	2	0
4	H	0.997214	0	109 353116	0	120.000000	0	1	2	3
Exp.[d]	1.012–1.024		106.7–107 8							
Theor.[e]	1.001–1.004		107.0–107 6							

[a] These are reproductions of 'archive files' generated by MOPAC and subsequently submitted to minor re-editing. In an archive file the molecular geometry is represented by an array of data called Z-matrix that is not a matrix in a mathematical sense, but it must fulfill a certain standard format (see Ref. 9).

[b] Ref. 12

[c] Ref. 7(a), 24 various levels of ab initio calculations from HF/6–31G* to MP2/6–31G*.

[d] Ref 13.

[e] Ref 15, various levels of ab initio calculations from HF/4–31G* to HF/6–31G**.

potential energy of 2-methyl-5(4*H*)-oxazolone are given in Table 1. Worthy of note is the apparently high value for the C(1)-C(2)-O(12) angle (136.3°) which is nevertheless in complete agreement with the value (135.9°) reported for an analogue [11]. As for the oxazolone, the initial geometries of both water and ammonia were assumed. Their refined geometries, charge distribution and energies are provided in Table 1, together with selected experimental [12,13] and theoretical [14,15] reference data for comparison.

While keeping both the reactant molecules completely stiff in their relaxed geometries, we applied one- and two-dimensional PATH, that is, we thoroughly scrutinized selected one- or two-dimensional projections from the six-dimensional space defined in terms of the variables from Fig. 1 (also compare, e.g., Table 2 vs. Table 1), while simultaneously allowing the remaining five or four variables to relax. For instance, we could simultaneously and independently vary a pair [r(13,2), φ(13,2,1,3)] or a pair [θ(13,2,1), φ(13,2,1,3)] while allowing the respective remainders of the variable sets to relax.

We found that the six-dimensional space was a multiple-minima space, and observed that at each minimum the interacting O- or N-nucleophile was invariably brought into a 'contact distance' with the azlactone carbonyl. The global minima were eventually localized; they are characterized in both the oxazolone/water and the oxazolone/ammonia complexes by rudimentary H-bonds connecting O(5) with H(14), and O(12) with H(15) (Fig. 1). In the oxazolone/ammonia complex there is a third H-bond connecting O(12) with H(16) so that O(12) appears to be a bifurcated atom. Subsequent unrestricted minimizations of the two complexes did not change the geometries nor the potential energies to any appreciable degree. The two minimum-energy encounter-complexes are shown in Fig. 2, whereas the pertinent geometrical parameters are given in Table 2. Even though the global minima were eventually found, the energy distributions among the global and many other local minima were not far from even, therefore we do not attach too much significance to the geometries shown in Fig. 2. On the other hand, such a situation would bring about

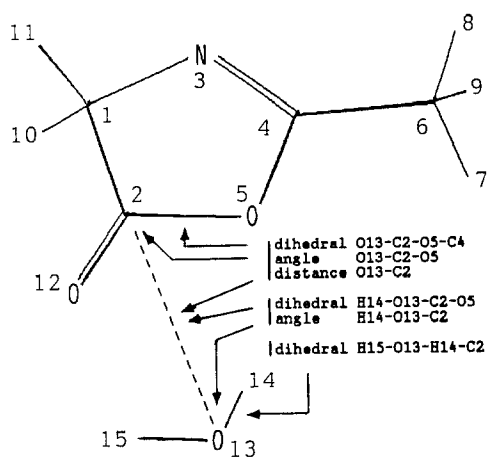

Fig 1 The numbering of the atoms (uniform for all the models considered) and the six variables defining the mutual positions of the reactants for the oxazolone/water encounter-complex. This numbering is different from IUPAC requirements that are O1-C2-N3, but it was not changed because it is the numbering that emerges directly from the program used (see Tables 1–4).

a positive, i.e., favorable, contribution to the entropy of complexation. The minimum-energy geometries of the products (*N*-acetylglycine and *N*-acetylglycine amide, respectively) were easier to determine since they could be found by a routine 2-dimensional grid search in the (φ, ψ) conformational space of the peptide backbone [16].

Subsequently, the reactant and product sets obtained were submitted to the SADDLE calculations, which led to unreasonably high energies of the transition states (TrSts) ($\Delta E^{+} \approx 49$–58 kcal/mol), clearly indicating that the hypothesis of an elementary single-step mechanism was invalid. An intermediate that would be compatible with the reactants and at the same time promise facile conversion to the product seemed to be the α-hydroxyimine (imidic acid, imidol) tautomeric form of the *N*-acetylglycine derivative. Accordingly, unstable imidic acid forms of AcGly and AcGlyNH_2 are henceforth considered as products of the first reaction step; their tautomerism to the parent amides is discussed in a subsequent paper.

The minimum-energy geometries of the imidol form of AcGly and AcGlyNH_2 were found by a similar grid search. They are presented in Fig. 3 while the respective geometrical parameters are given in Table 3. The pertinent values of $\Delta E^{+} \approx 27$–41 kcal/mol seemed acceptable this time.

Subsequently, separate SADDLE runs were carried out for the two reactant/product sets, and after refinement by the NLLSQ procedure, they resulted in the structures shown in Fig. 4 and Table 4. The distributions of charge are also given and they indicate that the TrSts are appreciably

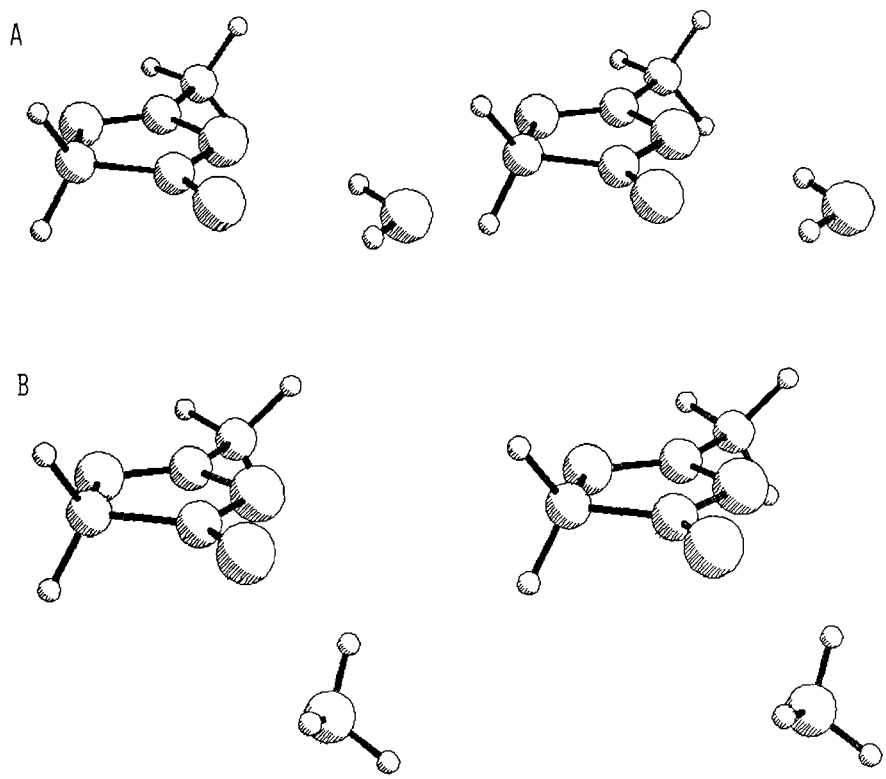

Fig. 2. Optimized geometries for A the oxazolone/water encounter-complex; B: the oxazolone/ammonia encounter-complex, in the ideal gas phase.

TABLE 2
AM1-OPTIMIZED GEOMETRIES[a], HEATS OF FORMATION AND CHARGE DISTRIBUTIONS IN THE ENCOUNTER-COMPLEXES

C4 H7 N O3
2-methyl-5(4*H*)-oxazolone + water
Fully optimized complex at 3.462 Å

Heat of formation = −114.028839 kcal/mol
Dipole = 3.91202 Debye
No. of filled levels = 23
Ionization potential = 11.187637 eV
Molecular weight = 117.104

No.	Final geometry obtained AM1 symmetry, T = 280 restart							Connectivities N1	N2	N3	Charge
1	C	0.000000	0	0.000000	0	0.000000	0	0	0	0	−0 1431
2	XX	1.000000	0	0.000000	0	0.000000	0	1	0	0	
3	C	1.525468	1	52.245145	1	0.000000	0	1	2	0	0.2747
4	N	1.460566	1	52.245145	0	180.000000	0	1	2	3	−0 1936
5	C	1.307853	1	108.185151	1	−0.028906	1	4	1	3	0 0917
6	O	1 426792	1	114.362800	1	0.042833	1	5	4	1	−0 2503
7	C	1 478847	1	131.753413	1	−179.934047	1	5	4	1	−0.1648
8	H	1.119030	1	109.175221	1	−119.978989	1	7	5	4	0.1180
9	H	1 118985	1	109 183519	1	121.306095	1	7	5	4	0.1187
10	H	1.117506	1	110.687169	1	0.654342	1	7	5	4	0.1200
11	H	1 122480	1	110.532463	1	−119.486398	1	1	4	5	0.1557
12	H	1.122591	1	110.525611	1	119 372596	1	1	4	5	0.1559
13	O	1.219592	1	136.704431	1	179.878749	1	3	1	4	−0.2780
14	O	3.463871	1	175.311287	1	73.777727	1	3	1	4	−0.4019
15	H	0.962372	1	34.755532	1	−83.324391	1	14	3	1	0.1970
16	H	0.962070	1	103.273178	1	9.262199	1	14	15	3	0 2001

C4 H8 N2 O2
2-methyl-5(4*H*)-oxazolone + ammonia
Fully optimized complex at 3.109 Å

Heat of formation = −60.918930 kcal/mol
Dipole = 1 61756 Debye
No of filled levels = 23
Ionization potential = 10.215098 eV
Molecular weight = 116.119

No.	Final geometry obtained AM1 symmetry, T = 280							Connectivities N1	N2	N3	Charge
1	C	0.000000	0	0.000000	0	0.000000	0	0	0	0	−0.1427
2	XX	1.000000	0	0.000000	0	0.000000	0	1	0	0	
3	C	1.526407	1	52.274743	1	0.000000	0	1	2	0	0.2786
4	N	1 460417	1	52.274743	0	180.000000	0	1	2	3	−0 1962
5	C	1 308025	1	108 091936	1	−0 336409	1	4	1	3	0.0911
6	O	1 424895	1	114.516761	1	0.446572	1	5	4	1	−0 2477
7	C	1.479065	1	131.496053	1	−179.116270	1	5	4	1	−0.1635
8	H	1.118348	1	109.400547	1	−132 607013	1	7	5	4	0.1134
9	H	1.119243	1	108.970688	1	108.559331	1	7	5	4	0.1176
10	H	1 117464	1	110.659607	1	−11.718507	1	7	5	4	0.1176
11	H	1 121853	1	110.599959	1	−119.944083	1	1	4	5	0.1504
12	H	1.122744	1	110.385953	1	118.754173	1	1	4	5	0.1568
13	O	1.218772	1	136.499888	1	−179.949254	1	3	1	4	−0.2730
14	N	3.114188	1	123.634530	1	84.050138	1	3	1	4	−0.4047
15	H	1 000141	1	56.891445	1	−125.797751	1	14	3	1	0.1376
16	H	0.999908	1	108.262993	1	47.828305	1	14	15	3	0.1373
17	H	0.998289	1	108.829335	1	118.105605	1	14	15	16	0.1275

[a] See footnote [a] to Table 1.

TABLE 3

AM1-OPTIMIZED GEOMETRIES[a]. HEATS OF FORMATION AND CHARGE DISTRIBUTIONS IN THE PRODUCTS

C4 H7 N O3
Acetyl-glycine tautomer
Optimized geometry

Heat of formation = −128.315573 kcal/mol
Dipole = 2.17513 Debye
No. of filled levels = 23
Ionization potential = 10.568807 eV
Molecular weight = 117.104

No.	Final geometry obtained AM1 symmetry, T = 280 precise							Connectivities N1	N2	N3	Charge
1	C	0 000000	0	0 000000	0	0.000000	0	0	0	0	−0.0606
2	XX	1.000000	0	0.000000	0	0.000000	0	1	0	0	
3	C	1.517723	1	57.879181	1	0.000000	0	1	2	0	0.2840
4	N	1 428041	1	57.879181	0	180.000000	0	1	2	3	−0 2840
5	C	1.296500	1	123.885633	1	−74 930539	1	4	1	3	0.1539
6	O	1.381307	1	128.937580	1	1.556989	1	5	4	1	−0 2939
7	C	1.506089	1	122.009970	1	−177.120682	1	5	4	1	−0.1705
8	H	1 117119	1	109.645624	1	−66.542189	1	7	5	4	0.1107
9	H	1 117119	0	109.645624	0	173.457811	0	7	5	4	0.1084
10	H	1.117119	0	109.645624	0	53.457811	0	7	5	4	0.1098
11	H	1.120617	0	110 505549	0	165.069461	0	1	4	5	0.1484
12	H	1 120617	0	110 505549	0	45.069461	0	1	4	5	0.0886
13	O	1.230163	1	128.835975	1	−120.394316	1	3	1	4	−0.3372
14	O	1 364333	1	114.158721	1	62.005513	1	3	1	4	−0 3466
15	H	0.969305	1	111.477655	1	10.349887	1	6	5	4	0.2358
16	H	0.970973	1	110 298725	1	−179.561905	1	14	3	1	0.2531

C4 H8 N2 O2
Acetyl-glycine amide tautomer
Optimized geometry

Heat of formation = − 78.719250 kcal/mol
Dipole = 2.53130 Debye
No. of filled levels = 23
Ionization potential = 10.206922 eV
Molecular weight = 116.119

No.	Final geometry obtained AM1 symmetry, T = 280 precise							Connectivities N1	N2	N3	Charge
1	C	0 000000	0	0.000000	0	0.000000	0	0	0	0	−0.0989
2	XX	1.000000	0	0 000000	0	0.000000	0	1	0	0	
3	C	1.542203	1	56.754423	1	0.000000	0	1	2	0	0 2737
4	N	1.430235	1	56.754423	0	180.000000	0	1	2	3	−0.2926
5	C	1 298115	1	122.431710	1	68.086164	1	4	1	3	0.1454
6	O	1.380491	1	128.618555	1	−2.079325	1	5	4	1	−0.2986
7	C	1.505455	1	122 199770	1	177.103490	1	5	4	1	−0 1701
8	H	1.117055	1	109.669230	1	−55.103151	1	7	5	4	0.1073
9	H	1.117055	0	109.669230	0	−175.103151	0	7	5	4	0.1091
10	H	1.117055	0	109.669230	0	64.896849	0	7	5	4	0.1065
11	H	1.120010	0	110.215189	0	−51.913836	0	1	4	5	0.1014
12	H	1 120010	0	110.215189	0	−171.913836	0	1	4	5	0.1186
13	O	1.250588	1	119.983916	1	−93.368527	1	3	1	4	−0 3985
14	N	1.364884	1	118.740477	1	86.742520	1	3	1	4	−0.4130
15	H	0 972899	1	111.665332	1	−7.745566	1	6	5	4	0 2482
16	H	0.990098	1	119.805769	1	−177 943715	1	14	3	1	0 2314
17	H	0.987612	1	120.705892	1	−6.258921	1	14	3	1	0.2301

[a] See footnote [a] to Table 1.

TABLE 4

AM1-OPTIMIZED GEOMETRIES[a], HEATS OF FORMATION AND CHARGE DISTRIBUTIONS IN THE TRANSITION STATES

C4 H7 N O3
2-methyl-5(4*H*)-oxazolone + water
Fully optimized TrSt yielded by the approach from 3.4 Å/ext− + tautomer

Heat of formation = −73.061787 kcal/mol
Dipole = 4.54203 Debye
No. of filled levels = 23
Ionization potential = 8.826713 eV
Molecular weight = 117.104

No.	Final geometry obtained AM1 NLLSQ cycles = 500, T = 540 restart							Connectivities N1	N2	N3	Charge
1	C	0.000000	0	0.000000	0	0.000000	0	0	0	0	−0.0118
2	C	1.513489	1	0.000000	0	0.000000	0	1	0	0	0.3415
3	N	1.414449	1	116.411169	1	0.000000	0	1	2	0	−0.4084
4	C	1.330542	1	119.696905	1	−13.762643	1	3	1	2	0.2112
5	O	1.304249	1	122.552914	1	−0.894099	1	4	3	1	−0.6362
6	C	1.505313	1	120.041019	1	178.715010	1	4	3	1	−0.1864
7	H	1.116598	1	108.635769	1	−141.571938	1	6	4	3	0.0954
8	H	1.116965	1	108.617582	1	100.123639	1	6	4	3	0.0862
9	H	1.115302	1	112.199284	1	−20.432308	1	6	4	3	0.0952
10	H	1.130750	1	105.328549	1	120.657654	1	1	2	3	0.1297
11	H	1.131250	1	106.246190	1	−123.993838	1	1	2	3	0.0980
12	O	1.206351	1	140.718992	1	−106.705168	1	2	1	3	−0.2281
13	O	1.520321	1	112.325035	1	77.721150	1	2	1	3	−0.2342
14	H	1.019232	1	109.507494	1	−42.466831	1	13	2	1	0.3479
15	H	0.987593	1	109.596912	1	−158.628640	1	13	2	1	0.3001

C4 H8 N2 O2
2-methyl-5(4*H*)-oxazolone + ammonia
Fully optimized TrSt yielded by the approach from 3.1 Å/helix L tautomer

Heat of formation = −33.764702 kcal/mol
Dipole = 7.62740 Debye
No. of filled levels = 23
Ionization potential = 8.276945 eV
Molecular weight = 116.119

No.	Final geometry obtained AM1 T=280 1SCF							Connectivities N1	N2	N3	Charge
1	C	0.000000	0	0.000000	0	0.000000	0	0	0	0	−0.0031
2	C	1.534140	1	0.000000	0	0.000000	0	1	0	0	0.2450
3	N	1.401110	1	119.602144	1	0.000000	0	1	2	0	−0.4540
4	C	1.330800	1	124.739956	1	7 446844	1	3	1	2	0.2279
5	O	1.293762	1	125.781983	1	−4.942395	1	4	3	1	−0.6108
6	C	1.513369	1	117.833422	1	176.092969	1	4	3	1	−0.1914
7	H	1 116254	1	108.375408	1	−140.409484	1	6	4	3	0.0916
8	H	1.116356	1	108.635218	1	101.449071	1	6	4	3	0.0772
9	H	1.114904	1	112.489057	1	−19.372166	1	6	4	3	0.0896
10	H	1.133416	1	103.633136	1	122.306620	1	1	2	3	0.1112
11	H	1.131909	1	106.144052	1	−124.180197	1	1	2	3	0.0774
12	O	1.221326	1	129.812532	1	−118.311316	1	2	1	3	−0.2387
13	N	1.511118	1	114.884414	1	61.127916	1	2	1	3	−0.1786
14	H	1.062114	1	104.261248	1	−79.326224	1	13	2	1	0.3131
15	H	1.016124	1	112 355195	1	161.407758	1	13	2	1	0.2161
16	H	1.015325	1	110.315439	1	37.469429	1	13	2	1	0.2277

[a] See footnote[a] to Table 1

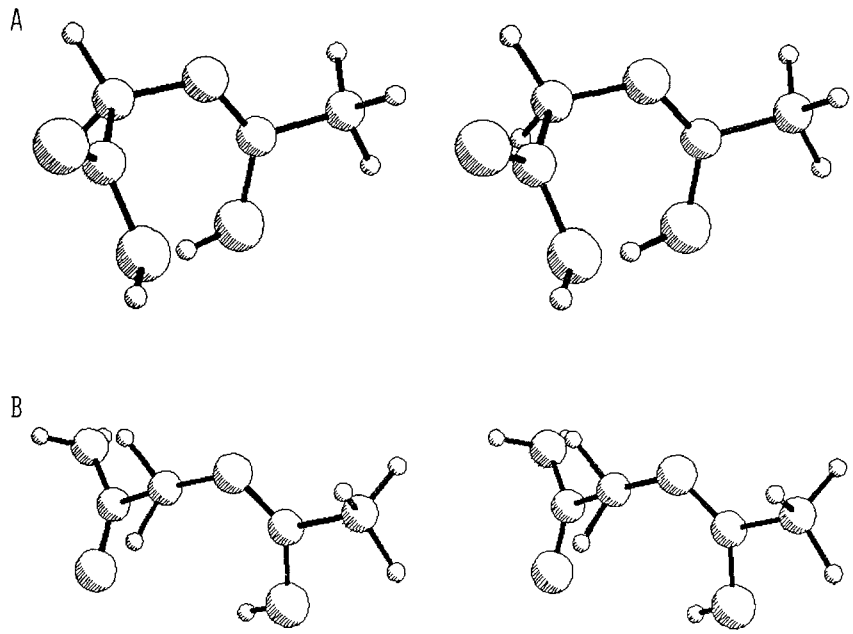

Fig. 3. Optimized geometries of A. the *N*-acetylglycine tautomer; B: the *N*-acetylglycine amide tautomer.

polarized relative to either the reactants or the products. These polarizations develop into a relative excess of negative charge (equal to ≈ 0.3 of electronic charge) on the leaving oxygen O(5), which is compensated by deficits of roughly equivalent electronic charge in either the protonated carboxy or carboxamido groups of the two products (see Tables 2–4).

Simulations of weakly-polar solvation shells

Peptide syntheses involving oxazolones are often carried out in aprotic solvents of weak to intermediate polarities such as dichloromethane (DCM) or tetrahydrofuran (THF) [1–3]. These solvents have dipole moments of 1.6 D [17] and estimated averaged molecular radii of 3.0 and 3.5 Å, respectively. For the purpose of simulating solvent effects, we made the following assumptions: the role of a solvent such as DCM or THF was considered passive at every stage of the reaction, i.e., the solvent was considered to provide the reacting species with their 'natural environment' without ever participating as catalyst or inhibitor. As such, the solvent had to form a cage or a shell around the reacting species, and it was assumed that a time-averaged distribution of the incident solvent molecules composing such a shell was spherically symmetrical.

We elected to simulate this solvation shell by means of a best-fitting number of identical balls placed at the vertices of a regular (platonian) polyhedron of optimized size, i.e., surrounding the reacting species by a sphere of optimized radius made up of balls of almost fixed radius. A dipole of 1.6 D was placed at the centre of each ball and the radius of a ball was constrained not to decrease below 3.5 Å while at the same time the radius of the cavity, providing space for the reacting species, was constrained not to exceed 10 Å. These constraints were equivalent to the statement that a polyhedron edge could not decrease below 7 Å while its radius or distance between its centre and a vertex could not exceed 10 Å. The only polyhedron reasonably fitting these constraints

appeared to be the regular eicosahedron, with 12 vertices and an edge-to-radius ratio equal to $5^{1/2}/(4 \cdot \sin 36) = 0.951$. A cube (eight vertices, edge-to-radius ratio equal to $1/3^{1/2} = 0.577$) would have had to be excessively expanded while a dodecahedron (20 vertices, edge-to-radius ratio equal to $1/2 \cdot \sin 18 = 1.618$) would have had to be squeezed prohibitively.

For the calculations, the previously optimized geometries of the reactants, the encounter-complexes, the TrSts, and the products were taken. They were surrounded by the solvation shells with the initial shell radii equal to 7 Å and their centres coincident with but not restricted to C(1) (see Fig. 1). Each system was then submitted to unrestricted optimization either by BFGS (the minima) or by NLLSQ (the saddle points). The refined geometries surrounded by the solvation shell did not differ considerably from those obtained for a vacuum. A notable exception was the oxazolone/water encounter-complex in which considerable mutual repositioning of each molecule took place. Such a change is in perfect agreement with the previous observation that in vacuo the energy distribution among various local minima involving the encounter-complexes was almost even. The eicosahedral shell of dipoles imitated quite well an external field that could *dynamically* give the impression of an almost perfect sphere; spinning the solvation shell around any chosen axis caused virtually no change in the energy of the system other than proper mutual reorientation of all the dipoles of the solvation shell.

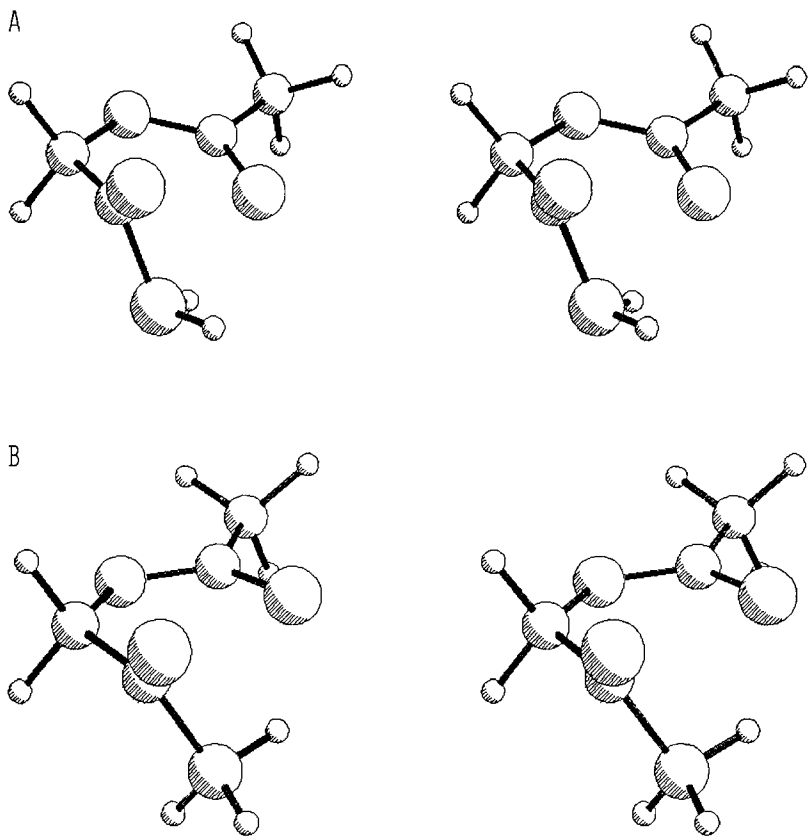

Fig. 4. Optimized geometries of the TrSts in the reactions of A: the oxazolone with water; B: the oxazolone with ammonia.

TABLE 5
SIMULATED EFFECTS OF 'SOLVATION' ON THE REACTION OF 2-METHYL-5(4*H*)-OXAZOLONE WITH WATER[a]

	Ox	W	Ox+W	Δ^0_{ec}	Ox·W	Δ^+	TrSt	Δ^0	P
R_{ss} (Å)	8 908	7.644	*	*	8.943	*	8.960	*	9.354
E_{svd} (kcal/mol)	−51.49	−60.69	−112.18	−3.27	−115.45	40.95	−74.50	−17 19	−129.37
E_{vac} (kcal/mol)	−50.30	−59.24	−109.54	−4 49	−114.03	40.97	−73.06	−18.90	−128.44
Δ (kcal/mol)	−1.19	−1 45	−2.64	1.22	−1.42	−0.03	−1 44	1.71	−0.93

[a] Ox, 2-methyl-5(4*H*)-oxazolone; W, water; e.c., encounter-complex; TrSt, transition state; Δ^+, energy difference between TrSt and Ox·W (e.c.); P, product; R_{ss}, solvation shell radius, svd, solvated; vac, in vacuo.

The energies of the reacting species in vacuo and in the 'solvent' are compared in Tables 5 and 6. The contribution of the electrostatic interaction among the dipoles themselves has been subtracted from the total energy so that the net charges in the heats of formation can be associated directly with the solvation effects. The optimized radii of the solvation shells are also given. It is seen clearly that the optimum sizes of the shells generally appear to be slightly larger than the 'theoretical' ones, whose radii would be $\approx 7.0 \times 0.951$ Å.

The data in Tables 5 and 6 indicate that, assuming heat of solvation and enthalpy are identical, a weakly polar solvent moderates the potential energy variations along the reaction path so that negative changes become less negative and positive changes become less positive (see columns headed by *). In their solvated states all stationary species along the reaction paths experience small decreases in potential energy, relative to their in vacuo counterparts, and these decreases range from 0.7 to 2.7 kcal/mol. It is clear that our solvation model neglects dispersion forces as well as the effect of the electric field of the bulky solvent; however, the former should be negligible at the distance of 9–10 Å while the latter should be about the same on all the objects involved in the reaction path. Hence, we believe that the observed *changes* in the solvation energy, essentially attributable to the cavitation only, reflect changes typical of weakly polar solvents. Finally, the calculated potential energy changes compare very favorably with typical heats of solvation [18].

TABLE 6
SIMULATED EFFECTS OF 'SOLVATION' ON THE REACTION OF 2-METHYL-5(4*H*)-OXAZOLONE WITH AMMONIA[a]

	Ox	A	Ox+A	Δ^0_{ec}	Ox·A	Δ^+	TrSt	Δ^0	P
R_{ss} (Å)	8.908	7.677	*	*	9.463	*	8.713	*	9 266
E_{svd} (kcal/mol)	−51.49	−8.76	−60 25	−1.64	−61.89	25.25	−36.64	−19 26	−79 51
E_{vac} (kcal/mol)	−50 30	−7.28	−57.58	−3 34	−60.92	26.94	−33.98	−21.22	−78.80
Δ (kcal/mol)	−1 19	−1.48	−2.67	1.70	−0 97	−1.69	−2.66	1.96	−0.71

[a] Ox, 2-methyl-5(4*H*)-oxazolone; A, ammonia; e.c., encounter-complex, TrSt, transition state; Δ^+ refers to the energy difference between TrSts and Ox A (e.c.); P, product; R_{ss}, solvation shell radius; svd, solvated; vac, in vacuo.

Evaluation of the results and the method

There have been several successful applications of the AM1 method for ground-state calculations [6–8], thus it can be applied with reasonable confidence. We have gathered much evidence confirming satisfactory performance of the method with respect to ground states. The question remains, however, as to how well the method might perform for TrSts, species for which the method was not and could not have been parameterized.

Despite the fact that there are no kinetic data on the reactions involved in the current analysis, an answer to the question ensues from the observations that at room temperature the reaction with ammonia is complete in seconds while that with water requires days for completion (unpublished results). Given an AM1-imbedded error as well as the fact that the rate constants project themselves logarithmically onto the Gibbs-energy scale, one can see immediately that misestimates by as much as two orders of magnitude in assumed reaction rates would alter the ΔG values by only 2.57 ($RT \times \ln 10^2 = 1.982 \times 300 \times 2.303 \times 2 \times 10^{-3}$) kcal/mol at 300 K, a value that is unlikely to bear heavily on the conclusions that follow.

Thus, assuming the half-life times for the second-order reactions of the oxazolone with water and ammonia to be five days and five s, respectively, at ideal-gas-state conditions corresponding to a concentration of 22.414^{-1} mol·dm^{-3}, typical of 1 mol at 1 atm, the rate constants are 5.19×10^{-5} and 4.48 dm^3·mol^{-1}·s^{-1}, which translate into Gibbs energies of activation of 23.63 and 16.58 kcal/mol, respectively. A question that arises at this point is whether a direct comparison of these Gibbs energy estimates with the HoF values generated by the AM1 method is permissible, or should the zero-point-energy and thermal-vibration-energy, both calculable within MOPAC, have been accounted for prior to the comparison. It is our opinion that the AM1 method, as parametrized against standard thermodynamic HoF at 25°C [5], already allows for these corrections. Hence, it is clear that in the present interpretation the AM1 method, though correctly predicting the *tendencies* for both reactions, overestimates the energy barriers ΔE^{+} by 13 and 7 kcal/mol for the reactions with water and ammonia, respectively.

Turning now from energetic to geometric/mechanistic considerations, it is clear that the method comes forth with quite reasonable mechanisms, compatible with common chemical experience, and as such if handled critically can be of value in delineating geometrical details of mechanisms and eliminating some pathways in favor of others. Specifically, both TrSts in Fig. 4 approximate the tetrahedral geometry at the former/future carbonyl carbon C(2) with the newly forming C(2)-O(N) (13) bonds already well developed and the C(2)-O(5) bonds to be broken still maintained, all of them being about 1.5 Å in length, i.e. exceeding their optimum lengths by 10%. It remains uncertain if there are any local zwitter-ionic minima near these TrSts. We could not detect any under the conditions imposed, corresponding either to a gas phase or to a weakly polar solvent.

CONCLUSIONS

The results demonstrate that the simple nucleophilic addition reaction involved in the ring-opening of oxazolones must be parsed into at least two steps, namely formation of the α-hydroxyimine (imidic acid), followed by its tautomerization to the parent acylamide. In the reaction of oxazolone with water, there occurs concerted formation of the O(13)-C(2) bond, disruption of the C(2)-O(5) bond and transfer of H from O(13) to O(5). In the reaction of oxazolone with ammonia, there occurs concerted formation of the N(13)-C(2) bond, disruption of the C(2)-O(5) bond

and transfer of H from N(13) to O(5) with consecutive rotation of $\approx 180^{\circ}$ about the C(1)-C(2) bond. No evidence for a two-step mechanism has been apparent in the observations on experimental work. In the accompanying paper it is demonstrated by the same techniques that the tautomerization imposes interesting geometrical requirements on the reacting species, and provides clues to the mechanism of formation of oxazolones.

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