The crystal structure of BeF$_3$-activated CheY, with manganese in the magnesium binding site, was determined at 2.4-Å resolution. BeF$_3$ bonds to Asp$^{57}$, the normal site of phosphorylation, forming a hydrogen bond and salt bridge with Thr$^{87}$ and Lys$^{109}$, respectively. The six coordination sites for manganese are satisfied by a fluorine of BeF$_3$, the side chain oxygens of Asp$^{13}$ and Asp$^{57}$, the carbonyl oxygen of Asn$^{59}$, and two water molecules. All of the active site interactions seen for BeF$_3$-CheY are also observed in P-Spo0A$^\dagger$. Thus, BeF$_3$ activates CheY as well as other receiver domains by mimicking both the tetrahedral geometry and electrostatic potential of a phosphoryl group. The aromatic ring of Tyr$^{106}$ is found buried within a hydrophobic pocket formed by $\beta$-strand $\beta_4$ and helix H4. The tyrosine side chain is stabilized by hydrogen bonding with a hydroxyl group of Glu$^{89}$. This hydrogen bond appears to stabilize the active conformation of the $\beta$/H4 loop. Comparison of the backbone coordinates for the active and inactive states of CheY reveals that only modest changes occur upon activation, except in the loops, with the largest changes occurring in the $\beta$/H4 loop. This region is known to be conformationally flexible in inactive CheY and is part of the surface used by activated CheY for binding its target, FliM. The pattern of activation-induced backbone coordinate changes is similar to that seen in FixJ$^\dagger$. A common feature in the active sites of BeF$_3$-CheY, P-Spo0A$^\dagger$, P-FixJ$^\dagger$, and phosphono-CheY is a salt bridge between Lys$^{109}$ N$^\ddagger$ and the phosphate or its equivalent, beryllofluoride. This suggests that, in addition to the concerted movements of Thr$^{87}$ and Tyr$^{106}$ (Thr-Tyr coupling), formation of the Lys$^{109}$PO$_2^-$ salt bridge is directly involved in the activation of receiver domains generally.

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of two other response regulators, Spo0A\(^r\) (21) and FixJ\(^r\) (22), have been reported (superscript \(r\) denotes receiver domain). Spo0A\(^r\) was unknowingly crystallized in the phosphorylated state with calcium as the divalent metal rather than magnesium, and FixJ\(^r\) was crystallized in the absence of a divalent metal ion to circumvent problems associated with hydrolysis of the phospho-aspartate. It is known that removal of magnesium from phosphorylated CheY does not alter its enhanced affinity for FlIM (23). This suggests that, while magnesium is important in the chemistry of phosphorylation of receiver domains, it is probably not required for stabilizing the active conformations. Thus, the structures of P-Spo0A\(^r\) and P-FixJ\(^r\) do likely represent the phosphorylation-activated states, although the activities of these two proteins in the conditions used for crystallization cannot be directly assessed. Importantly, the residues homologous to Thr\(^{87}\) and Tyr\(^{108}\) in both structures adopt significant conformations to those seen in the NMR structure of BeF\(_3\)-CheY.

We have recently determined the crystal structures of BeF\(_3\)-CheY and BeF\(_3\)-CheY complexed with a 16-residue peptide derived from the N terminus of FlIM. The binding interactions of the CheY-peptide complex have been discussed (24). Herein we report the crystal structure of BeF\(_3\)-CheY complexed with the divalent cation manganese solved at 2.4 Å resolution. A detailed comparison of the active sites of BeF\(_3\)-CheY and P-Spo0A\(^r\) (21) clearly shows that BeF\(_3\)-aspartate activates receiver domains by reproducing the geometry and electrostatic potential of a phospho-aspartate. Indeed, all of the active site interactions in BeF\(_3\)-CheY are identical to those in P-Spo0A\(^r\), indicating that the structural changes induced by BeF\(_3\) activation of response regulators are the same as those induced by phosphorylation. We also show, through a comparison of backbone coordinates of BeF\(_3\)-CheY with inactive magnesium-bound CheY, that activation results in only relatively small structural differences, except in loops, and that these differences are similar in magnitude to those observed between inactive and phosphorylated FixJ\(^r\) (22).

MATERIALS AND METHODS

*Escherichia coli*—CheY was overexpressed and purified as described previously (20, 25) and was prepared as a solution containing 2 mM CheY, 8 mM BeCl\(_2\), 50 mM NaF, and 4 mM MnCl\(_2\) at pH 8.4. Crystals of the complex were obtained at room temperature using the hanging-drop vapor diffusion method using a well solution containing 1.8 M ammonium sulfate, 5–10% glycerol, and 100 mM Tris (pH 8.4). The crystallization droplets contained the CheY solution mixed with an equal volume of the well solution. Crystals appeared after 1 day and grew to \(-0.7 \times 0.4 \times 0.4\) mm after 3 days. The concentration of glycerol in the well solution was increased (5% at each step) every 2 days to a final concentration of 25 volume %.

The structure of BeF\(_3\)-CheY was determined to 2.4 Å resolution by molecular replacement (MR) using AMoRe (27). The structure of BeF\(_3\)-CheY was obtained from the Protein Data Bank accession code 1F4V, which was used as the search model with Tyr\(^{108}\) replaced by alanine. Two solutions were easily found with a correlation coefficient of 67% and an R-factor of 34% (20–3.5 Å). The MR solution refined with several rounds of simulated annealing and B-group refinements using CNS (28) to an R-factor and R-free of 29.5% and 31.4%, respectively. Structure factors (\(F_I\) and \(F_o\)) were calculated from this partially refined MR model using SFALL of the CCP4 package (29). These phases were improved by 20 rounds of 2-fold noncrystallographic symmetry averaging and solvent flattening at 2.4 Å using the RAVE package (30), with a mask made from the MR solution and operators from the MR solution refined by the IMP program using the 2\(F_o\) – \(F_I\) MR map. In each round the map was calculated using coefficients 2\(F_o\) – \(F_I\) with \(F_o\) and \(F_I\) calculated from the density-modified map of the previous cycle.

An unbiased (2\(F_o\) – \(F_I\)) map calculated with phases and \(F_I\) from the final symmetry-averaged, solvent-flattened map was displayed using the graphics program O (31) and used as a guide in modeling Tyr\(^{108}\), positioning Mn\(^{2+}\) ions, and manually modifying the model in places where it did not fit the electron density. Refinement was performed using CNS (28). Anisotropic R-factor and bulk solvent corrections as well as the cross-validation method (32) were applied throughout the refinement. From 15.0 to 2.37 Å data were included in the refinement with tight noncrystallographic symmetry restraints (300 kcal mol\(^{-1}\) Å\(^2\)). Water picking was performed after the R-factor and R-free dropped to 24%/27% using CNS.

The electron density for beryllium fluoride on Asp\(^{87}\) was clearly seen (10 σ) in the resulting CNS \(F_o\) – \(F_I\) SIGMAA weighted map. This moiety was modeled on both protoners and refinement continued giving a final R-factor and R-free of 21/0.24%. Geometric parameters for the structure were monitored using PROCHECK (33) and WHAT_CHECK (34).

RESULTS AND DISCUSSION

BeF\(_3\)-CheY crystals were grown in the presence of manganese (Mn\(^{2+}\)). Although *in vivo* CheY is complexed with magnesium (Mg\(^{2+}\)), NMR studies have shown that the active site readily accommodates larger divalent cations (12, 35). Given that Mn\(^{2+}\) has the same coordination geometry as Mg\(^{2+}\) and supports phospho-transfer from CheA-P to CheY (11), we expect that it does not perturb the active structure significantly.

BeF\(_3\)-CheY complexed with Mn\(^{2+}\) crystallized in the space group P2\(_1\)2\(_1\)2\(_1\) and diffracted to 2.4 Å. The two molecules in the asymmetric unit form a noncrystallographic symmetric dimer (Fig. 1) similar to that seen for P-FixJ\(^r\) (22), with helix H4 of one molecule packing against the H4-β5-H5 face of the second molecule. For CheY, dimer formation in the crystal must be due to lattice packing forces and is not biologically relevant, because in solution BeF\(_3\)-CheY remains monomeric even at 3 mM protein concentrations. Refinement statistics are summarized in Table I.

The overall crystal structure of BeF\(_3\)-CheY retains the (βα)\(_5\) fold of receiver domains (6) (Fig. 1) and is very similar to the NMR structure of BeF\(_3\)-CheY (20) as well as the crystal structure of inactive Mg\(^{2+}\)-bound CheY (36). Superposition of Cα coordinates (residues 6–125) of the BeF\(_3\)-CheY x-ray structure with the mean BeF\(_3\)-CheY NMR structure and the Mg\(^{2+}\)-bound CheY x-ray structure yielded root mean square deviations of only 1.2 and 0.8 Å, respectively. Differences in Cα coordinates between BeF\(_3\)-CheY and the crystal structure of inactive Mg\(^{2+}\)-bound CheY, based on a superposition of the residues least affected by activation, are shown in Fig. 2. The biggest changes are observed in the β4/H4 loop, the β5/H5 loop, and the N terminus of helix H5. The significance of the changes in the β4/H4 loop are particularly hard to interpret, because it adopts different conformations in the various crystal structures.
Comparison of the BeF$_3$-activated CheY active site with those of phosphorylated receiver domains determined to high resolution, including P-Spo0A$'$ (21), P-FixJ$'$ (22), and phosphono-CheY (38), provides a structural basis by which phospho-aspartate acts as a ligand to the divalent metal atom, forms a salt bridge with Lys$^{109}$ N$_\alpha$ and hydrogen bonds with Thr$_{87}$ O$_\gamma$ and the backbone amides of Trp$_{58}$, Asn$_{59}$, and Ala$_{80}$. The measured distances for the common interactions in the structural models of BeF$_3$-CheY and P-Spo0A$'$ are within coordinate uncertainties ($\pm 0.3$ Å) (Table II). It appears that, although calcium has an extra coordination site relative to manganese (and magnesium), which is occupied by a water molecule in P-Spo0A$'$, the extra ligand is accommodated without requiring a significantly different active site geometry.

Although lacking a divalent cation, the distances for the analogous interactions in P-FixJ$'$ are also similar to those seen for BeF$_3$-CheY and P-Spo0A$'$ (Table II). The only exception is the large distance (4.1 Å) between Lys$_{109}$ N$_\alpha$ and Asp$_{12}$ O$_\alpha$ in P-FixJ$'$, indicating that this salt bridge is broken in the ab-

of inactive CheY (6). Indeed, dynamics studies of Mg$^{2+}$-bound CheY showed that this region is flexible in solution (37), and a superposition of the x-ray structure of BeF$_3$-CheY with the NMR structures of Mg$^{2+}$-bound CheY shows that the $\beta_4$H4 loop of the active (x-ray) structure falls on the edge of the bundle formed by the inactive (NMR, Mg$^{2+}$-bound) structures. Rather than a conformational change, we prefer to view the activation-induced changes in the $\beta_4$H4 loop as a stabilization of the active conformation that may be sampled by the inactive protein. Unfortunately, it is hard to make similar conclusions for the $\beta_5$H5 loop, because the relaxation data for residues in this loop could not be reliably interpreted due to complications caused by chemical exchange of Mg$^{2+}$ in the active site (37).

Active Site of BeF$_3$-CheY—From the NMR structure of BeF$_3$-CheY we determined that the switch from an inactive to an active conformation involves hydrogen bond formation between the hydroxyl group of Thr$_{87}$ and an active site residue (Fig. 3). Of these, BeF$_3$-Asp$_{77}$. As a consequence of, or in conjunction with, formation of this hydrogen bond, $\beta$-strand $\beta_4$ (along with Thr$_{87}$) is displaced, and the aromatic ring of Tyr$_{106}$ becomes buried in a hydrophobic pocket between helix H4 and $\beta_5$. However, the NMR data did not define the positions of either the BeF$_3$ moiety or the divalent cation. In addition, the NMR data for Lys$_{109}$, a residue known to be critical for switching to the active conformation (10), were insufficient to define the positions of those pair of structures.

Active Site Comparisons with P-Spo0A$'$, P-FixJ$'$, and Phosphono-CheY—Comparison of the BeF$_3$-activated CheY active site with phosphate-CheY (38), provides a structural basis by which phospho-aspartate acts as a ligand to the divalent metal atom, forms a salt bridge with Lys$_{109}$ N$_\alpha$ and hydrogen bonds with Thr$_{87}$ O$_\gamma$ and the backbone amides of Trp$_{58}$, Asn$_{59}$, and Ala$_{80}$. The measured distances for the common interactions in the structural models of BeF$_3$-CheY and P-Spo0A$'$ are within coordinate uncertainties ($\pm 0.3$ Å) (Table II). It appears that, although calcium has an extra coordination site relative to manganese (and magnesium), which is occupied by a water molecule in P-Spo0A$'$, the extra ligand is accommodated without requiring a significantly different active site geometry.

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### Table I

| Crystal: | Space group | P2$_1$2$_1$2$_1$ |
|---------|-------------|-----------------|
|         | Cell dimensions $a$, $b$, $c$ | 53.3, 53.8, 161.2 Å |
| Data collection (cryogenic): | Resolution limit (Å) | 2.4–2.37 |
|         | Measured reflections | 89,177 |
|         | Unique reflections | 17,703 |
|         | $R_{sym}$ (%) (overall/last shell) | 7.5/23.0 |
|         | Completeness (%/last shell) | 89.1/52.2 |
|         | Average $B$-factor (Wilson 2.4–3.0 Å) | 45.4 |
| Refinement: | No. of molecules in AU | 2 |
|         | No. of amino acids | 256 |
|         | No. of solvent molecules | 173 |
|         | Resolution used (Å) | 15.0–2.37 |
|         | Sigma cutoff | 0.0 |
|         | No. of reflections work/test | 16748/846 |
|         | Final $R$-factor/$R_{int}$ ($|F| > 0$) | 21.0/24.0 |
|         | Average $B$-factor ($Å^2$) | 44.8 |
|         | Root mean square deviations from ideal geometry | |
|         | Bond lengths (Å) | 0.011 |
|         | Bond angles (degree) | 1.5 |

* The resolution range in the highest bin is 2.41–2.37 Å.
ence of metal. It is interesting to note that, although a divalent cation is necessary for the chemistry of phosphorylation and dephosphorylation of CheY, removal of the metal after phosphorylation apparently does not alter the affinity of P-CheY for FliM (23). Similarly, the fact that P-FixJr purifies as a dimer in the absence of metal, consistent with its activated state, suggests that the metal is not required for inducing the active conformation of FixJr. This may be a general feature of receiver domains.

In phosphono-CheY, except for the salt bridge between Lys\textsuperscript{109} N\textsubscript{z} and a phosphonate oxygen, the distances measured for the analogous hydrogen bonds are outside of the acceptable range (2.5–3.1 Å) (Table II). The absence of these interactions leads to much smaller changes in the β4/H4 and β5/H5 loops (Fig. 2c). The modest structural differences relative to inactive CheY appear to be consistent with the partial activity of phosphono-CheY, which shows an 8-fold increase in affinity for N16-FliM (38), whereas BeF\textsubscript{3}– and phosphorylation-activated CheY show a 25-fold increase in affinity (19, 39). Considering that the Sγ–Cδ bond in phosphono-cysteine is only 0.5 Å longer than the Cγ–Oδ bond in phospho-aspartate, it is surprising that the phosphonate analog does not better activate CheY. Since the salt bridge formed by Lys\textsuperscript{109} N\textsubscript{z} and an active site partner (BeF\textsubscript{3}–, PO\textsubscript{3}–, phosphonate) is the only common interaction in P-Spo0A\textsuperscript{r}, P-FixJr, BeF\textsubscript{3}–-CheY, and phosphono-CheY, it appears to be an important part of the active site interactions that together induce the fully active conformation. Based on crystal structures of mutant forms of CheY, it was previously

**Fig. 3. Stereo view of the active site of BeF\textsubscript{3}–-CheY.** Carbon, nitrogen, oxygen berylliofluoride, and manganese atoms are colored gray, dark blue, red, yellow, and green, respectively. a, omit map contoured at 3.0 σ covering Asp\textsuperscript{12}, Asp\textsuperscript{13}, BeF\textsubscript{3}–-Asp\textsuperscript{57}, Thr\textsuperscript{87}, Lys\textsuperscript{109}, and two water molecules. This map was calculated with the occupancies for these residues set to zero. For clarity, the density for manganese is not shown. b, ball-and-stick diagram of the BeF\textsubscript{3}–-activated CheY active site. Dashed lines and numbers denote active site interactions defined in Table II. c, stereo view of active site residues for BeF\textsubscript{3}–-CheY(Mn\textsuperscript{2+}) (blue), phosphorylated FixJr(no metal) (lime), and phosphorylated Spo0A(Ca\textsuperscript{2+}) (copper). Mn\textsuperscript{2+} and Ca\textsuperscript{2+} are shown as red and green balls, respectively. Residue numbers are based on *E. coli* CheY. For clarity, phosphono-CheY was not included.
suggested that Lys\textsuperscript{109} plays a role in positioning the \(\beta5/H5\) loop (40, 41).

Activation-induced Conformational Changes—CheY and FixJ\(^r\) are the only receiver domains that have been solved with sufficient resolution in both active (22) and inactive (36, 42) states to allow a detailed comparison of activation-induced structural changes. The largest activation-induced Cα coordinate changes for both proteins occur in loop regions, particularly the \(\beta4/H4\) loop. In addition, the \(\beta5/H5\) loop shows significant displacement in CheY, potentially due to the Lys\textsuperscript{109} \(\rightarrow\) BeF\textsubscript{3} salt bridge, but the analogous conformational change is not seen in FixJ\(^r\). As stated previously, for inactive CheY the \(\beta4/H4\) loop is conformationally flexible in the inactive state and becomes stabilized upon activation.

Even though the loops show significant activation-induced changes, activation of CheY and FixJ\(^r\) does not result in any major structural rearrangements. Whereas some \(\beta\)-strands and \(\alpha\)-helices are slightly displaced, the actual residues that define these elements of secondary structure remain unchanged in both proteins. In both BeF\textsubscript{3}-CheY and P-FixJ\(^r\) the N terminus of H4 moves slightly upon activation, and in CheY there is also a small displacement of the N terminus of H5. Indeed, even when compared as a group (Fig. 4), including P-Spo0A\(^r\), there are no dramatic structural differences among either the active or inactive forms of the receiver domains. Although there are small differences in the tilt and inclination of the helices, these differences do not give rise to changes in atomic coordinates of more than a few Ångstroms.

The structures of Spo0A\(^r\) and NtrC\(^r\) have also been determined in both the active (21, 43) and inactive states (44, 45). It was difficult to analyze the activation-induced structural changes for Spo0A\(^r\), because the inactive form crystallized as a domain-swapped dimer, the biological relevance of which is unclear. In contrast to CheY and FixJ\(^r\), the low resolution NMR structures of active and inactive NtrC\(^r\) show major structural differences, especially for residues that define helix H4. A higher resolution structure of BeF\textsubscript{3}-activated NtrC\(^r\) will more clearly define these changes.

Conclusions—The comparable interactions in the active sites of BeF\textsubscript{3}-CheY and P-Spo0A\(^r\) indicates that BeF\textsubscript{3}-aspartate is almost a perfect structural mimic of phospho-aspartate. In conjunction with our previous biochemical data that show functional activation of receiver domains with BeF\textsubscript{3} (19, 20), it appears that beryllium fluoride is a convenient tool that can be applied to biochemical as well as structural studies of a host of response regulators. Given the high sequence conservation, it is perhaps not surprising that the structures of P-Spo0A\(^r\), P-FixJ\(^r\), and BeF\textsubscript{3}-CheY all show similar interactions in the active site. Based on a comparison of these structures we can begin to define a general mechanism of activation. As predicted by previous biochemical and genetic studies on CheY, the hydroxyl group of Thr\textsuperscript{57} (Thr\textsuperscript{53} Spo0A\(^r\), Thr\textsuperscript{52} FixJ\(^r\)) (13) and the side chain of Lys\textsuperscript{109} (Lys\textsuperscript{106} Spo0A\(^r\), Lys\textsuperscript{104} FixJ\(^r\)) (10) form what appears to be critical active site interactions with the phosphoryl group (or BeF\textsubscript{3}). As a consequence of, or in conjunction with, these interactions, Tyr\textsuperscript{106} (Phe\textsuperscript{103} Spo0A\(^r\), Phe\textsuperscript{101} FixJ\(^r\)) adopts a buried conformation. Just how general these three events are is in the transition from an inactive to an active conformation and how they affect the overall structures of receiver domains generally remains to be determined.

Comparison of just crystal structures suggests that there is a coupling between phosphorylation of CheY and FixJ with structural changes, especially in the \(\beta4/H4\) loop. The extent to which phosphorylation induces an actual conformational change versus a stabilization of the active state from a pre-existing equilibrium between the active and inactive conformations in solution is not clear. Positive evidence for the idea of stabilization comes from NMR studies of inactive, constitutively active mutant forms (46), and phosphorylated NtrC (43), which indicate that phosphorylation stabilizes the active conformation (47). Additional NMR and x-ray studies of active and inactive forms of response regulators will help to clarify this issue and will help define how phosphorylation-induced conformational changes ultimately regulate the diverse processes controlled by two-component signal transduction.

### Table II

| Active sites distances (Å) |
|---------------------------|
| **BeF\textsubscript{3}-CheY** | **P-Spo0A\(^r\)** | **P-FixJ\(^r\)** | **Phospho-CheY** |
| 1. PO\textsubscript{3} - Thr\textsuperscript{57} O\textsubscript{γ} | 2.5 | 2.5 | 2.7 | 6.4 |
| 2. PO\textsubscript{5} - Ala\textsuperscript{88} | 2.9 | 2.8 | 3.0 | 4.3 |
| NH | 3. PO\textsubscript{5} - Lys\textsuperscript{109} | 2.9 | 3.0 | 3.1 | 3.0 |
| NH | 4. Lys\textsuperscript{109} | 2.8 | 2.6 | 4.1 | 5.8 |
| NH - Asp\textsubscript{12} O\textsubscript{δ} | 2.6 | 2.5 | N/A | N/A |
| CO | 5. Asp\textsubscript{12} O\textsubscript{δ} - H\textsubscript{2}O | 2.4 | 2.6 | N/A | N/A |
| NH | 6. M\textsuperscript{2+} - H\textsubscript{2}O | 2.4 | 2.6 | N/A | N/A |
| NH | 7. M\textsuperscript{2+} - PO | 2.2 | 2.6 | N/A | N/A |
| NH | 8. M\textsuperscript{2+} - Asp\textsubscript{13} O\textsubscript{δ} | 2.3 | 2.6 | N/A | N/A |
| CO | 9. M\textsuperscript{2+} - Asn\textsuperscript{59} | 2.3 | 2.5 | N/A | N/A |
| NH | 10. PO\textsubscript{3} - Asn\textsuperscript{59} | 3.0 | 2.9 | 2.9 | 5.5 |
| NH | 11. PO\textsubscript{3} - Trp\textsuperscript{26} | 2.9 | 2.9 | 3.4 | 5.9 |
| NH | 12. M\textsuperscript{2+} - Asp\textsuperscript{57} | 2.2 | 2.6 | N/A | N/A |
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